Remarks/Arguments

Reconsideration and allowance of the above-referenced application are respectfully requested.

Claim Status

Claims 1, 2, 9, 14-16, 19, 25, 28, 37-39, 51, 52, 59, 66 and 68-86 are pending. Claims 4 and 27 have been canceled without prejudice. Claims 1, 2, 9, 14, 15, 16, 19, 25, 28, 37-39, 51, 59, 66, 68 and 70-78 have been amended, and new claims 79-86 have been added. Basis for the amendments to claim 1, 28, 37 and 78 can be found in various parts of the specification including paragraph 12 (extended functional lifespan), paragraph 13 (biological interaction – claim 1), paragraph 14 (implant system – claim 1) and paragraph 76 (sensor). Basis for the amendment to claim 14 can be found in paragraph 20 of the specification, as well as other parts of the text. The amendments of independent claims 37 and 78 reciting cell culture derived basement membrane have basis in various parts of the specification, including paragraph 105.

Dependent claims 2, 9, 15, 16, 19, 25, 51 and 66 have been amended to be consistent with amended claim 1. Claims 38, 39, 59 and 74-77 have been amended to be consistent with claim 37. Claim 68 has been amended to recite a glucose sensor. Claims 70-73 have been amended to be consistent with claim 28. The addition of "biological system" to claim 78 has basis in paragraph 166 of the specification. New claims 79-85 contain language similar to claims 9, 68, 14, 16, 59, 66 and 76, respectively. New claim 86 has basis in various parts of the specification, including paragraph 130.

The specification has been amended to correct a few typographical errors and to further summarize some of the data depicted in Fig. 38.

Telephone Interview

The applicant acknowledges with appreciation the courtesy of the Examiner in holding a telephone interview on January 13, 2010. The applicant believes that progress was made in the interview in resolving some of the issues raised by the Examiner in connection with claim language.

Claim Rejection Under 35 U.S.C. 102

Claims 1, 2, 4, 9, 14-16, 19, 25, 27, 28, 37, 39, 51, 52, 54, 68, 69, 70, 72 and 73 stand rejected, and claims 76-78 are also rejected in the September 9, 2009 Office Action, under 35 U.S.C. 102(e) as being anticipated by Sayler et al. (U.S. Patent No. 6,673,596; filed Dec. 2, 1999). Reconsideration is requested.

The Office Action contends that cols. 23, 35, 17 and 3 of Sayler recite a matrix material that reads on the "biological matrix" recited in independent claims 1 and 28 of the present application, as well as the language used in former versions of independent claims 37 and 78. Each of these portions of Sayler is described below and is also discussed in the attached Rule 132 Declaration of Donald Kreutzer. A discussion of other parts of Sayler describing matrices and/or coatings also is included below, and is incorporated into the Declaration of Donald Kreutzer.

Use of the Terms "Biocompatible Container" and "Bioreporter Container" in Sayler

The Sayler Patent describes a bioluminescent bioreporter integrated circuit device (BBIC) configured to detect analytes in fluid when implanted in the body of an animal. The BBIC contains a biological component (whole cells) that functions as a bioreporter, and an analytical measuring element, such as an integrated circuit. The bioreporter emits light when it is exposed to an analyte. The Sayler patent uses the word "container" when referring to the "biocompatible container" and also when referring the "bioreporter container." The two containers are different from one another. The "biocompatible container" is the container that contains the entire implantable device (col. 3, lines 39-42), and is designated as 20 on Fig. 2. The "bioreporter container" is the container for the bio-reporter and is designated as 22 on Fig. 2. Furthermore, the Sayler patent uses the term "biocompatible housing" (col, 6, line 11 and Fig. 2) interchangeably with biocompatible container (col. 3, lines 40-43). For clarification purposes, the biocompatible container as the "biocompatible container/housing" in this Supplemental Amendment.

Summary of Sayler Disclosure

In Sayler, the biocompatible container/housing 20 is described in cols. 3, 6, 10 (lines 46-48), 17 and 25, and the bioreporter container 22 is described in cols. 4, 10 (lines 42-46), 23, 31 and 35. The bioreporter container also is described in claims 2-4 of Sayler.

In the discussion that follows, the relevant portions of Sayler are considered in the order in which they appear in the text of Sayler, except for Sayler's disclosure of Matrigel, which is discussed first below. Matrigel is a cell culture derived basement membrane material. Matrigel is used in the Examples of the present application, and cell culture derived basement membrane is claimed in the amended version of independent claims 37 and 78 of the present application.

Use of the Term "Matrigel" in Sayler

The only specific disclosure of any type of basement membrane in Sayler is in **Example 7, col. 35**. This portion of Sayler indicates that cell culture derived basement membrane (Matrigel) is used **inside** the bioreporter device, **not as a surface coating in contact with body tissue** (see col. 35, lines 42-48). More particularly, Matrigel is employed as a glue to support cells in compartment 22 to promote the sensing function of the device. Col. 35, lines 42-48 of Sayler state: "*Biochips may be coated with Matrigel, a basement membrane material that promotes attachment of epithelial cells. An alternative approach suspends the cells in Matrigel and allows it to form a gel on the surface of the biochip. The cells are then immobilized in the basement membrane material and are not subject to dislodgement by friction.*" In Sayler, the Matrigel clearly is not in contact with the biological tissue in which the BBIC is implanted. The reference to attachment of Matrigel to epithelial cells is not suggesting that the Matrigel would attach to body tissue in the Sayler embodiment, but instead explains why the Matrigel will function as a glue to hold the irradiated human tumor cells, hepG2 and Hela, in place on the biochip. The hepG2 and Hela cells are tumorgenic (i.e. the cause tumors when injected into tissue) which is why they are irradiated to prevent them from dividing, which is what tumor cells want to do. Additionally, irradiation, at levels that allow cell survival, cannot guarantee that 100% will not divide, thus it is possible that dividing

tumor cells could survive the irradiation dose used for this type of procedure. A semi-permeable membrane is a membrane that allows passage of certain molecules or ions, especially small molecules or ions, but acts as a barrier to larger substances. One would need to use a semi-permeable membrane to cover the cells in the embodiment described in col. 35 of Sayler for a number of reasons:

> First, the cells are **human tumors** and you would not want them getting out of the device and causing cancer in the body tissue. In fact it is known that cells, including tumors, can migrate through basement membranes *in vivo* and through Matrigel *in vitro* (BD BioScience) and thus without a semi-permeable membrane between the body tissue and the cells (attached by Matrigel), the reporter cells including tumor cells can migrate away from the reporter chip, resulting in loss of bio-reporter function. In the absence of a semi-permeable membrane the tumorgenic tumor cells can invade the host tissue and potentially result in tumor formation.
>
> Second, without a semi-permeable membrane on the bioreporter chip, the tumor cells will cause blood vessels to grow into the reporter chip and interfere with reporter function, i.e. the red blood cells will interfere with the fluorescence measurements, and the blood vessels will mechanically dislodge the tumor cell for the reporter surface. (In contrast, as recited in the independent claims in the present application, the growth of vessels **enhances** the <u>function of the sensor by bringing blood close to the sensor</u>.)
>
> Third, the semi-permeable membrane would be needed to prevent at least some of the cells (whether or not they are tumor cells) from being killed by the body's immune system (by innate and acquired immunity).
>
> Fourth, if the chip was placed on the surface of a endoscope (as Sayler proposes as one possible use) and was used to hunt for tumor cells inside a human body, one would need a semi-permeable membrane so that the cells would not be rubbed off the device and deposited in the body. If deposition occurred the device would not function and again one would run the risk of inducing cancer at the sites where the tumor cells were "rubbed off" the endoscopic device.

Matrigel does not function as a semi-permeable membrane and therefore could not be used as the semi-permeable membrane in the embodiment described in col. 35 of

Sayler. Thus, col. 35 of Sayler does not disclose, and furthermore **teaches away from,** the use of Matrigel to encapsulate the bioreporter (cells) when no semi-permeable membrane is used, i.e. when the biological matrix (basement membrane) is in contact with **both** an outer surface of an implantable device **and also** with a biological system, as is recited in independent claims 1, 37 and 78 of the present application. Furthermore, col. 35 of Sayler teaches away from the use of cells in a matrix to extend the functional lifespan of a sensor, as is recited in claims 1 and 28, and in the alternative in claim 37.

Exhibit 5 of the attached Declaration of Dr. Kreutzer shows additional reasons why the Matrigel cell adhesive of Sayler cannot be in contact with both body tissue and the implant even if the cells in the bioreporter are not tumor cells. First, the sensor would not function due to interference by autofluoroescence (akin to the difficulty of seeing a polar bear (fluorescence of bioreporter) in a snowstorm (tissue autofluoroescence)). Matrigel itself has autofluoroescence, and entrapping the cells in Matrigel is akin to throwing a white tent over the polar bear in a snow storm. Furthermore, as indicated above, Matrigel is not a semi-permeable membrane but rather a gel or paste. If an attempt were made to use Matrigel as a semi-permeable membrane in a bioreporter system involving fluorescence cell reporters, the result would be failure of the bioreporter and device because of the following effects: **1)** tissue injury induced by the implantation of the device would cause inflammation which in turn would degrade the Matrigel and result in destruction of the bio-reporter cells as a result of invading inflammatory cells; **2)** Matrigel would not prevent leakage of toxic materials out of the sensor into the tissue, i.e., the toxic substances would kill or injure tissue cells, resulting in even more inflammation and fibrosis resulting in destruction of the bioreporter; **3)** Matrigel would not prevent the migration of the fluorescence cells themselves out of the bioreporter, **4)** Matrigel would not prevent the invasion of blood vessels into the bioreporter resulting in both the dislodging of the fluorescent bioreporter cells from the surface, as well as introducing blood into the bioreporter chamber which would block detection of the fluorescence bioreporter cells; **5)** Matrigel would not block the movement of antibodies or complement proteins into the bioreporter, resulting in

destruction of the reporter cells directly and promoting complement and leukocyte mediated cell reporter cell killing; **6)** Matrigel would not block complement, antibody or leukocyte bystander killing of nearby tissue cells, resulting in release of toxic substance form the reporter cells; **7)** pus would accumulate in the sensor. Pus contains leukocytes, which would kill both reporter cells and nearby tissue cells, again triggering more inflammation and the release of toxic substance from the reporter cells; and **8)** the leukocytes also contain/release powerful proteases which would rapidly destroy the matrigel and the bio-reporter cells.

Disclosure of "Polymer Matrix" and "Hydrogel" in Sayler

According to **col. 3, lines 39-42** of Sayler, the implantable device "[p]referably is contained in a biocompatible container[/housing]." **Col. 3, lines 43-44** state that the biocompatible container/housing can comprise (a) silicon nitride, (b) silicon oxide, or (c) a suitable **polymer matrix,** such as polyvinyl alcohol, poly-L-lysine or alginate. According to claim 2 of Sayler, if a polymeric matrix is used, the function of the matrix is to keep the bioreporter cells in place over the integrated circuit. According to **col. 3, lines 46-48**, the polymer matrix may also further comprise a microporous hydrogel, a mesh-reinforced hydrogel or a filter-supported hydrogel. Basement membrane is NOT mentioned in col. 3 of Sayler and thus this portion of Sayler does not anticipate or render obvious independent claims 37 and 78, both of which recite cell culture derived basement membrane. As explained above, Matrigel does not function as a semi-permeable membrane as this term is used in Sayler. Furthermore, this portion of Sayler does not disclose the presence of **cells** in a matrix, and therefore does not anticipate or render obvious independent claims 1, 28 and 37 of the present application, all of which recite the presence of cells in the matrix.

Disclosure of "Semi-Permeable Membrane," "Selectively Permeable Membrane" and "Selectively Permeable Matrix" in Sayler

Although the Office Action does not cite col. 4 and 6 of Sayler, a discussion of these portion of Sayler are included for the sake of completeness and to support subsequent explanations of other portions of Sayler below. The bioreporter container is described in cols. 4 and 6 of Sayler. More particularly, Sayler provides that in order for

the BBIC to function, either the bioreporter container must include a semi-permeable membrane **(col. 4, lines 52-59)**, or the portion of the biocompatible container/housing that covers the bioreporter container must include a semi-permeable membrane **(col. 6, lines 11-18)**. The semi-permeable membrane is constructed to allow the analyte to enter the BBIC ***and*** to prevent the bioreporter cells and/or their toxic byproducts from exiting the BBIC. (Col. 4, lines 55-59 and col. 6, lines 13-18). Thus, in the embodiments of Sayler that are described in cols. 4 and 6, after implantation, the contents of the bioreporter container are **separated from** body tissue by the semi-permeable membrane and in some cases also (or instead) by the biocompatible container/housing. Stated another way, in the first case, the contents of the bioreporter container are separated from body tissue by a semi-permeable membrane that is part of the bioreporter container. In the second case, the contents of the bioreporter container are separated from body tissue by a semi-permeable membrane that is part of the biocompatible container/housing. In the third case, there is a first semi-permeable membrane that is part of the biocompatible container/housing and a second semi-permeable membrane that is part of the bioreporter container.

Col. 6, lines 18-24 of Sayler provide that "[t]he *bioreporter may be in solution, that is a cell suspension, and entrapped in the container by the semi-permeable membrane, or alternatively the bioreporter may be encapsulated in a selectively permeable polymer matrix that is capable of allowing the selected substance in solution reach the bioreporter. Preferably, the matrix is optically clear."* This portion of Sayler indicates that if there is a semi-permeable membrane holding the bioreporter cells in the bioreporter container, a selectively permeable matrix is not needed. However, if there is no semi-permeable membrane holding the bioreporter cells in the bioreporter container, a selectively permeable polymer matrix is required "that is capable of allowing the selected substance in solution to reach the bioreporter." This embodiment is also described in claims 2-4 of Sayler. Fig. 2 of Sayler depicts a semi-permeable membrane 21 (col. 10, line 65) which prevents bioreporter cells from leaving the bioreporter container (col. 4, lines 55-59) and Fig. 10C of Sayler shows an optional "selectively permeable membrane." While Sayler does not define "selectively permeable matrix,"

this term generally refers to a matrix that will allow only specific types of molecules through. Thus, in Sayler, either a semi-membrane layer, or a selectively permeable matrix that performs essentially the same function as a semi-permeable membrane, is used to keep out toxins, antibodies, pus, etc., and is positioned between body tissue and the bioreporter cells. In contrast, independent claims 1, 37 and 78 of the present application provide that a cell-containing biological matrix is **in contact with** both the implantable device and biological system and therefore there is no semi-permeable membrane or selectively permeable matrix separating the implantable device from the biological system. Claims 37 and 78 of the present application provide that the biological matrix comprises cell culture derived basement membrane, which is not a semi-permeable membrane or a selectively permeable matrix, because it will let all sizes of molecules through. Claims 1 and 28 of the present application (and claim 37 in the alternative) provide that the cells in the matrix extend the functional lifespan of the sensor, which is not the case in Sayler.

Col. 10, lines 42-48 of Sayler provide that the bioreporters are "*entrapped in a container behind a semi-permeable membrane*" or are "*encased in a polymer matrix.*" This portion of Sayler then further states that *"[t]he BBIC **is** enclosed in a biocompatible housing with a semi-permeable membrane covering the bioreporter region. This membrane allows glucose to pass to the bioreporters, yet stops the passage of larger molecules that could interfere with the glucose measurement.*" (emphasis added). Col. 10 of Sayler does not disclose or suggest an implant system in which a biological matrix is in contact with both an implantable device and biological (body) tissue (claims 1, 37 and 78). Furthermore, this portion of Sayler does **not** describe a matrix (in contact with an outer surface of an implantable device) containing cells that extend the functional lifespan of a sensor (claim 28 of the present application).

Disclosure of "Biocompatible Coverings and Coatings for Implants" in Sayler

Column 17, lines 46-67 of Sayler discuss biocompatible coverings and coatings for implants and prosthetic devices that can be used to either coat or form the housing. Suitable materials that are mentioned to minimize capsule formation and prevent physiological rejection of the implant include a thin biocompatible carbon film, a three-

dimensionally woven or knitted fabric of organic fibers, the coverings disclosed in US. Patent Nos. 5,653,755, 5,779,734 and 5,814,091. Collagen coating, and albumin coating. U.S. Patent Nos. 5,653,755 and 5,779,734 describe implant coverings made from fluoropolymer filaments attached to a stretch fabric backing. U.S. Patent No. 5,814,091 describes a two layer capsule for a medical implant comprising a first layer of a biocompatible material such as titanium and a second layer of a substantially diffusion-proof and corrosion-resistant metal. None of the materials described in this part of Sayler constitutes a "biological matrix" <u>supporting "a plurality of cells</u>", as is recited in independent claims 1, 28 and 37 of the present application. Furthermore, none of the materials described in this portion of Sayler constitutes a <u>plurality of cells associated with a cell culture derived basement membrane</u>, as is recited in independent claims 37. Finally, none of the listed materials in this portion of Sayler constitutes "<u>cell culture derived basement membrane</u>", as is recited in independent claim 78. A useful analogy to distinguish between naturally occurring basement membrane and cell culture derived basement membrane is the following: if naturally occurring basement membrane is considered to have an order 3D structure with specific composition and layers i.e. a "orderly brick wall with specific 3D structure," cell culture derived basement membrane that is **extracted** from cultured cells in vitro would be viewed as "a loose pile of bricks" , i.e. the pile of bricks has some of the same components as the wall, but the bricks have lost their specific (3D) relationship to each other, analogous to some of their function. Thus, column 17 of Sayler clearly does not disclose or suggest the cell culture derived basement membrane recited in independent claims 37 and 78 of the present application.

As indicated above, Matrigel is a cell culture derived basement membrane. Sayler does not disclose or suggest the use of Matrigel to form, cover or coat the biocompatible container/housing. The only use of Matrigel in Sayler is ***inside*** the bioreporter container, as is explained above in paragraph 13.

Cell Culture Derived Basement Membrane as Defined in the Present Application is not a Semi-Permeable Membrane

<u>**Col. 23, lines 32-56 of Sayler**</u> refer to two different embodiments. One

embodiment is a biosensor consisting of bioengineered cells entrapped in suspension behind a semi-permeable membrane. This first embodiment is shown in Fig. 10C (Fig. 10C has a notation of an optional membrane). The second embodiment is a biosensor consisting of cells encapsulated in a matrix. The second embodiment either is shown in Fig. 10B, is the version of Fig. 10C that does not include the membrane, or is not depicted in the drawings. Independent claims 37 and 78 of the present application provide that the membrane which contacts the outer surface of the implant **is cell culture derived basement membrane**. Cell culture derived basement membrane is NOT a "semi-permeable membrane" as this term is used in connection with the first embodiment of Sayler, <u>because it would not keep fluorescent or other toxic materials inside the sensor of Sayler and would not keep antibodies and pus out of the sensor of Sayler.</u> Moreover, the cell culture derived Matrigel used to support cells **inside** the semi-permeable membrane 21 of Sayler (as described at col. 35, lines 39-48 of Sayler) is not "in contact with an outer surface of the implantable device" as is required in claims 1, 37 and 78 of the present application because the outer surface of this portion of the BBIC requires a membrane or matrix to keep out antibodies and other bio-reporter toxic substances, and does not contain cells that extend the functional lifespan of the sensor (claim 28).

The second embodiment of Sayler described at **<u>column 23, lines 32-56</u>** provides that as an alternative to the use of a semi-permeable membrane, the biosensor may "consist of cells encapsulated in a polymeric matrix." Suitable matrices that are listed in Sayler are polyvinyl alcohol, sol-gel and alginate. Lines 52-55 in col. 23 of Sayler specifically mention polyvinyl alcohol mesh reinforced or microporous filter supported hydrogels. This portion of Sayler acknowledges that when no semi-permeable membrane is used, the encapsulating material must function as a membrane that protects the bioreporter from substances in the tissue and protects the tissue from toxic substances originating in the bioreporter. As indicated above, cell culture derived basement membrane would not function as a semi-permeable membrane as the term "semi-permeable membrane" is defined in Sayler, and thus Sayler does not disclose, and teaches away from, the use of cell culture derived basement membrane, as is

recited in claims 37 and 78. Furthermore, this portion of Sayler does not disclose or suggest a biological matrix **in contact with both biological tissue and an implantable device**, as is recited in claims 1, 37 and 78. Finally, this portion of Sayler does not disclose or suggest a matrix containing cells that extend the functional lifespan of a sensor, as in recited in claims 1 and 28 of the present application, and in the alternative in claim 37.

Hydrogel Membranes in Sayler Block Access of Immune System Components

Col. 25, lines 14-26 of Sayler state that host rejection effects can be minimized by enclosing cells in hydrogel membranes. Sayler states that the hydrogels "block access by the humoral and cellular components of the host's immune system but will remain permeable to the target substance glucose. Matrigel and cell culture derived basement membrane cannot be encompassed in this description of hydrogel membranes because Matrigel will not block access by antibodies. Furthermore, Matrigel is not likely to block the access of immune cells for any length of time, but instead will simply slow the entry of immune cells if a thick layer is used. Matrigel is a jelly-like substance, and antibodies will go right thru this type of matrix. Examples of suitable hydrogel materials provided at col. 25, lines 22-25 of Sayler are mesh-reinforced polyvinyl alcohol hydrogel bags. Col. 25, lines 26-37 mention that it may be necessary to provide a barrier between the cells and the appropriate body fluid. There is no mention of basement membrane or cell culture derived basement membrane in col. 25 of Sayler. Furthermore, there is no mention in col. 25 of Sayler of a matrix containing cells that extend the functional lifespan of a sensor.

Additional Disclosure of Semi-Permeable Membranes in Sayler

Col. 31, lines 33-37 of Sayler state that "[i]t may be necessary to isolate the bioreporters using a semi-permeable membrane to allow the transport of small molecules such as glucose and insulin across the membrane and prohibit the influx of immune effector cells and antibodies. . . . However, small molecules such as cytokines can still enter the selective membranes and interfere with the bioluminescent reporter cell lines. This approach has been used extensively by those of skill in the art." The quoted portion of Sayler further supports the teaching in Sayler that either a semi-

permeable membrane, or a "selectively permeable membrane" (or "selectively permeable matrix") that functions as a semi-permeable membrane, is required to keep unwanted materials out of the bioreporter portion of the sensor.

There is No Disclosure in Sayler of a Matrix in Contact with Both an Implantable Device Comprising a Sensor and with a Biological System (Claim 1) that Supports Cells Which Extend the Functional Lifespan of the Sensor (Claims 1 and 28)

As mentioned above, an important distinction of the system of the present application over each portion of Sayler directed to the biocompatible container/housing, is that the cells in the matrix of the system as recited in claims 1 and 28 of the present application, and as recited in the alternative in claim 37, **extend the functional lifespan of the sensor.** The biological materials described in Sayler (at col. 17, lines 62-67 of Sayler) as promoting some type of biocompatibility between the implant and the body (although there is no mention of extended functional lifespan) are collagen and albumin, neither of which constitutes "cells" in a biological matrix (claims 1, 28 and 37 of the present application).

There is No Disclosure in Sayler of a Matrix Comprising Cell Culture Derived Basement Membrane in Contact with a Biological System (Claims 37 and 78)

The collagen and albumin described at col. 17 of Sayler do not constitutes cell culture derived basement membrane (claims 37 and 78 of the present application). The hydrogel mentioned at col. 25, lines 14-25 of Sayler blocks access of components of the host's immune system, which is different from the structure and function of the cell culture derived basement membrane in the present application.

Thus, claims 1, 2, 4, 9, 14-16, 19, 25, 27, 28, 37, 39, 51, 52, 68, 69, 70, 72, 73 and 76-86 are not anticipated by Sayler. Reconsideration is requested.

Claim Rejection Based Upon 35 USC 103

Claims 28, 37, 38, 59, 66, 70, 71 and 74 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sayler et al. (U.S. Patent No. 6,673,596; filed Dec. 2, 1999), in view of Soykan et al. (U.S. Patent Application Publication No. 2001/0000802; effective filing date: Dec. 20, 2000). Reconsideration is requested.

The deficiencies of the Sayler patent are discussed above. The Soykan Patent is cited in connection with the rejection of independent claims 28 and 37, as well as several dependent claims. Soykan describes an implantable system for drug delivery to treat a disease, not to promote compatibility of an implant with body tissue. The Office Action indicates that Soykan is cited for its disclosure of endothelial cells that line the walls of blood vessels and that secrete vasodilatory, thrombolytic or angiogenic factors, such as vascular endothelial growth factor (VEGF). This document does not make up for the above-noted deficiencies of Sayler in that it <u>does not disclose cells that extend the functional lifespan of a sensor, as is recited in claims 1 and 28 of the present application</u>. Instead, the cells extend the lifespan of the person in whom the device is implanted by treating coronary artery disease, cerebral vascular occlusion, or the like. Furthermore, Soykan <u>does not disclose a matrix material comprising cell culture derived basement membrane that is in contact with both a sensor and biological system</u> as is recited in claims 37 and 78 of the present application, and thus does not make up for the deficiencies of Sayler.

Secondary Considerations

The attached Declaration of Dr. Kreutzer also explains how the embodiments that are claimed in the present application fulfill a long unmet need in producing glucose sensors having an extended lifespan. The claimed technology enables glucose sensors to be used more economically, also requiring fewer insertions into the skin of a patient each month.

Thus, claims 28, 37, 38, 59, 66, 70, 71 and 74 are not obvious over the combination of Sayler and Soykan. Reconsideration is requested.

Amino Acid Sequence Disclosure Requirements

An ASCII readable version of the sequence listing depicted in Fig. 22 is enclosed herewith.

Supplemental IDS

A Supplemental IDS also is enclosed.

In view of the above, it is believed that this application is in condition for allowance, and such a Notice is respectfully solicited.

Respectfully submitted,

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